EVALUATION OF THE EFFECTS OF LUMEFANTRINE COMPONENT OF COARTEM ON ELECTRICAL CONDUCTIVITY OF THE HEART IN PATIENTS TAKING COARTEM IN MANAGEMENT OF UNCOMPLICATED MALARIA IN KIU-TH BUSHENYI DISTRICT

BY

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DECLARATION

I BABIRYE PHIONA, declare that this report is my original copy and has never been presented to any other institution / university of learning for approval for any degree/diploma/certificate award for which it is now being proposed for.

SIGNATURE---PBiona---------- DATE-27: 03: 2015.

APPROVAL

This is to certify that this research report has been prepared under my supervision and has never been presented anywhere for other purpose and is now ready for submission to the school of pharmacy of Kampala International University

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DEDICATION

This work is dedicated to the Almighty and Everlasting king of glory who has enabled me come up with this report.

ACKNOWLEDGEMENT

The completion of this work is not only a fulfillment of my dreams but also a fulfillment of my parents' dreams of me becoming a professional and as an appreciation of their endless support towards my studies.

I am grateful to my esteemed supervisor for his courage and advice indulged in this project and hoping for the best outcome from this project.

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ABSTRACT

Background: Approximately 2.37 billion people live in areas at risk for transmission 0f *p.falciparum* malaria, mainly in sub-Saharan Africa **(Hay, et al., 2009).**

Combination Artemether/Lumefantrine (Coartem, Riamet, and Falcynate-LF) is a fixed dose Artemisinin-based combination therapy (ACT) indicated for the treatment of acute uncomplicated *Plasmodium falciparum malaria.* It is an effective and well tolerated treatment providing high cure rates even in areas with multi-drug resistance. Cardiac effect on electrical conductivity in terms of QTc prolongation and arrhythmias remains a matter of worry **(Lefevre, et al., 2001).**

Aim: Several unrelated drugs have pro-arrhythmic activity associated with an ability to prolong the QT-interval of the Electrocardiogram just as proved for Halofantrine (**Nosten, et al., 1993**). Lumefantrine has some chemical similarities to Halofantrin,(**Jatakiya,et al.,2014**),an antimalarial known for QTc prolongation and due to their structural similarities, also the cardiac effect on electrical conductivity of the heart by Lumefantrine remains a matter of debate in therapeutics. This research aimed at evaluating the effects of Lumefantrine component of coartem on electrical conductivity of the heart in patients taking coartem in management of malaria in KIU-TH Bushenyi District.

Method: The research was a quantitative prospective random study. Safety assessment was done by monitoring vital signs, blood pressure, Heart rate and monitoring of Electrical conductivity. Electrocardiograms were recorded before dosing and after the fifth dose. The QT interval and Heart rate were used to calculate QTc interval using Bazett's formula QTc=QT/RR1/2.The QTc interval as the response variable was compared between treatments.

Results; In the baseline electrocardiograms the QTc intervals were normal.

There was no clinically relevant differences in the QTc intervals observed after sequential administration ofArtemether/Lumefantrine(Coartem). No significant observation suggestive of cardiotoxicity was noted in the study.

Conclusion; The alternative hypothesis stating that Artemether /Lumefantrine possesses significant effect on electrical conductivity of the heart has not been supported by the results obtained in this study. Artemether/Lumefantrine can be used as a therapeutic option with likely better patient compliance in the treatmentofuncomplicated*P.falciparum*malaria.

CHAPTER ONE

1.0 Introduction

An estimated 2.37 billion people live in areas at risk for transmission of P. falciparum malaria, primarily in sub-Saharan Africa, Central and South America, Southern Asia, and Papua New Guinea (Hay, *et al.*, 2009).

A wide range of treatment options are available for the treatment of uncomplicated P. falciparum malaria. Drug resistance is a major impediment to the treatment of P. falciparum malaria. In the majority of regions where P. falciparum predominates, the parasites are resistant to common antimalarial drugs such as Chloroquine and Sulphadoxine + Pyrimethamine (SP) (World Malaria Report, 2008).

The commonly used therapies such as Quinine and Mefloquine are associated with tolerability problems. Another alternative, Atovaquone-Proguanil, although apparently well tolerated, has not been well studied, and the results are not encouraging. Moreover, resistance to these more recent treatment options is emerging (Guidance for Industry, 2003).

The six-dose regimen of Artemether-Lumefantrine is a good choice for treating acute and uncomplicated P. falciparum malaria because of its high efficacy, rapid resolution of clinical symptoms, and good tolerability. The safety, efficacy and pharmacokinetics for the fixed-dose combination when given in a single dose of Artemether 80 mg and Lumefantrine 480 mg (4 tablets of Coartem®) in different regimes have been evaluated and proved in various clinical trials across the world involving hundreds of patients of acute and uncomplicated P. falciparum malaria. These were controlled comparative clinical trials involving a large number of patients of malaria. The safety and efficacy data obtained from all of these clinical trials conclude that Artemether/Lumefantrine combination in a single dose of 80/480 mg respectively is effective and safe in the treatment of malaria (Falade *et al.*, 2008).

As per the recommendations, 4 tablets of the fixed-dose combination of Artemether/Lumefantrine (20/120 mg) should be given at 0hr and 8hrs on day 1 and morning and evening on days 2 and 3 in adults having body weight of more than 35 kg (Omari *et al.*, 2005).

Thus, the patient needs to consume a total of 24 tablets to complete the prescribed dose. Consumption of such a large number of tablets makes the "patient compliance" poor. In order to enhance the patient compliance, which is a critical step in improving the clinical outcome, a fixed-dose combination of Artemether and Lumefantrine (80/480 mg), maintaining the same ratio of 1:6 of Artemether and Lumefantrine is formulated. The rationale for designing such fixed dose combination was to offer the equally efficacious alternative with an improved patient compliance in the treatment of uncomplicated P. falciparum malaria for adult patients with a body weight of more than 35 kg.

Due to the structural similarity between Lumefantrine and Halofantrine, Lumefantrine is thought to produce cardiac effect similar to Halofantrine. Cardiac effect in electrical conductivity in terms of QTc interval prolongation and arrhythmias always remained a matter of worry (Lefèvre *et al.*, 2001).

Drugs that prolong QT interval including antimalarials such as Quinine and Quinidine should be used cautiously following the Artemether / Lumefantrine combination due to the long elimination half-life of Lumefantrine (3 to 6 days) and the potential for additive effects on the QT interval (Product monograph: Coartem® -Artemether/Lumefantrine, 2004).

Long QT syndrome, where the rate-correlated QT interval (QTc) of the ECG is abnormally long may be either congenital in origin or acquired, due to the effects of certain drugs.

A diverse range of drugs has been associated with the acquired long QT syndrome and some cause serious cardiac arrhythmias such as *Torsade de pointes* (Napolitano, *et al., 1994).* Concern has been expressed about the antimalarial drug Halofantrine following reports of QTc prolongation episodes of torsade de pointes or sudden cardiac death (Nosten *et al.*, 1993).

Although some of these adverse events occurred in patients with congenital long Syndrome (Toiven *et al.*, 1994). Halofantrine induced QT prolongation also occurred in individuals with normal Intervals (Monlune *et al.*, 1995). In addition adverse effects of Halofantrine have been observed in patients receiving higher doses (Karbwang *et al.*,1993) .,suggesting that the problem may not be confined to situations of overdose and was confirmed that Halofantrine caused prolonged QTc interval(*Am J, 2007).*

Artemether/Lumefantrine may cause a condition that affects the heart rhythm, QT prolongation, which can result in serious irregular heart beat and other symptoms. The risk of QT prolongation can be increased by

certain medical conditions or taking other drugs that may affect heart rhythm in that precautions are indicated in heart failure, slow heart rate, sudden cardiac death.(*FDA Med Watch,2014).*

Low levels of potassium and magnesium in the blood may also increase risk of Prolongation and this Artemether/Lumefantrine product may contain inactive ingredients which cause allergic reactions or other problems (*FDA Med Watch, 2014).*

*A*t present it's not known how Artemether/ Lumefantrine can cause such effects. A number of other drugs that prolong the QT interval do so as a consequence of direct actions on cardiac ion channels (Tan *et al., 1995). Alternatively it has bee*n suggested that the precipitation of arrhythmias such as *torsade de pointes* may result from an abnormal response to alterations in autonomic control of the heart. Increased adrenergic activity has been implicated in some types of long QT Syndrome. Whereas some ventricular tachycardias such as torsade de pointes can be a consequence preceding bradycardia.

Marked hypokalemia can also cause QT prolongation, trigger torsade de pointes and exacerbate the pro-arrhythmic effects of certain drugs, such as class 1a anti-arrhythmic (*Ben, David and Zipes, 1993, Tan et al., 1995). Thus* if Lumefantrine drug causes QT prolongation, then a number of mechanisms may contribute to the development of associated severe arrhythmias like *torsedes de pointes*. In addition the precipitation of serious arrhythmias may be more likely in the presence of confounding factors such as hypokalemia and bradycardia.

The aim of this research was to evaluate the effect of Lumefantrine component of coartem on electrical conductivity of the heart in patients taking coartem in management of uncomplicated malaria in Bushenyi district

1.2 Problem Statement

Halofantrine has been found to elongate depolarization QT wave in patients taking halofantrine (Norvatis et al., Eur J Clin Pharmacol 2000) but no work has been done in patients taking lumefantrine on the effect on electrical conductivity.

Artemether/Lumefantrine may cause a condition that affects the heart rhythm, QT prolongation which can infrequently result into serious though rarely fatal fast/ irregular heart beat and other symptoms such as dizziness, fainting that require immediate medical attention. (*FDA Med Watch.2014)*

Lumefantrine has some chemical similarity to Halofantrine (Jatakiya etal.2014) an antimalarial known for prolongation of QTc interval and since Lumefantrine has limited experience though in the same group with Halofantrine then its effect on the cardiovascular system required evaluation.

1.3 Purpose of the research

To evaluate the effect of Lumefantrine component of coartem on electrical conductivity of the hear t in management of uncomplicated malaria in Bushenyi district.

1.3.1 General objective

- To find out whether Lumefantrine elicits significant effects in electrical conductivity of the heart in patients with no heart problems.
- To find out whether Lumefantrine increases electrical conduction effects in patients taking Coartem
- To identify the effect of Coartem on the electrical conductivity of the heart.

1.3.2 Specific objective

- To find out the changes in the PQRST wave
- To identify the effect of this Coartem drug on QT intervals.

- To determine prolongation of QTc in patients taking Coartem.
- To evaluate acute effect of Artemisinin Combination Therapy on electrical conductivity in the heart.

1.4 Hypothesis

Null; Lumefantrine does not have cardiovascular effects on patients taking coartem.

Alternative Lumefantrine has significant effect on the cardiovascular system of a patient taking coartem tablets.

1.5 Justification of the study

Numerous studies have been carried out in various parts of the world about the use of coartem in management of *P.*falciparum malaria infection. However no studies have been done to exhaustively identify the cardiovascular effect in electrical conductivity caused by lumefantrine a component in coartem drug in management of malaria commonly used in Bushenyi District. This study was therefore important in that it intended to identify the commonly experienced cardiovascular effects in electrical conduction during use of coartem in malaria management in Bushenyi district and find possible solutions to address such problems.

CHAPTER TWO

2.0 Literature review

Malaria infection still remains a burden particularly among children in the sub-Saharan Africa. Data of annual 300-500 million clinical cases worldwide and ninety percent mortality in tropical Africa demands much attention even with the introduction of combination therapies (White, *et at.*, 1999). Malaria is one of the most significant causes of morbidity and mortality worldwide, causing approximately 881,000 deaths every year (WHO. 2008). The current WHO guidelines for the treatment of malaria recommend the use of Artemisinin based Combination Therapy owing to the rising threat of *Plasmodium falciparum* resistance to monotherapy (WHO. 2006).

Resistance to antimalarial drugs has been observed as one of the greatest problems in the control of malaria in Africa. This drawback cut across most antimalarials irrespective of their classes. However, the value of malarial therapy using combinations of drug has been identified as a strategic and viable option in improving efficacy, and delaying development and selection of resistance (Mayxay, *et al.*, 2004).

It is quite interesting to note that drugs may not be entirely safe in all patients, even when they have been reported safe in some regions they could still be influenced by sex, age, race, disease, body weight, and pharmaceutical dosage forms. The risk associated with their use in pregnancy and children below five years as the most afflicted groups in malarial scourge demands much attention in order to reduce the burden. Meanwhile, for a drug considered to be safe, its side-effects should be within the tolerable limit of the individual. Ideally, rare cases of toxicities and adverse reactions are expected to occur during post-marketing surveillance (http://rbm.who.int).

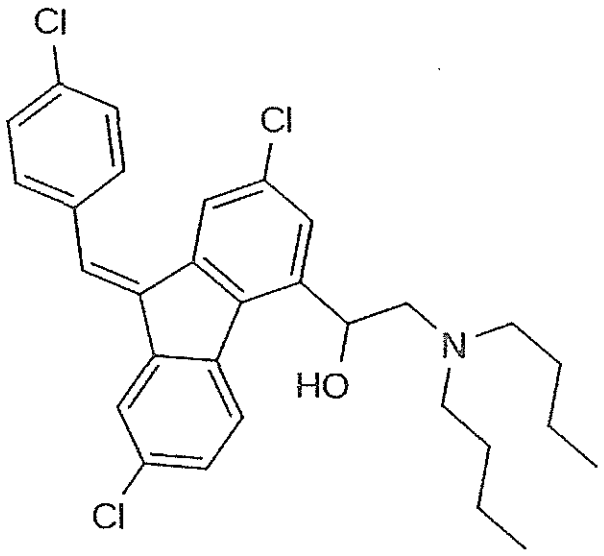
The combination Artemether/Lumefantrine (cortemr,Riamet) is a fixed dose combination Atemesinin based Combination Therapy indicated for treatment of uncomplicated p. falciparum and is very effective and well tolerated malaria treatment providing high cure rates of malaria even in areas of multi drug resistance as a result of its approval on the world essential drug list.(FDA Med Watch, 2014).

Artemether is a methyl-ether derivative of dihydroartemisinin, derived from Artemisinin (Qinghaosu). Artemether, and the closely related compound Arteether, given in high doses by intramuscular injection prolong the QTc-interval in rats and dogs which has given rise to concern that similar effect, could occur in clinical use ((Brewer, Grate and Peggins, 1994).

Lumefantrine is a drug with structural similarities to Mefloquine and Halofantrine. Its marketed in combination with Artemether for treatment of malaria and it appears to be effective and well tolerated but experience is limited.(Jatakiya, *et al.*,2014).

Artemether and Lumefantrine (COARTEM) is a new combination effective against multidrug resistant falciparum malaria. Lumefantrine is a racemic fluorene derivative with the chemical name 2-dibutylamino-1-[2, 7-dichloro-9-(4-chlorobenzylidene)- 9H-fluoren-4-yl]-ethanol. It conforms structurally, to the aryl-amino alcohol group of antimalarials including Quinine, Mefloquine, and Halofantrine. Other antimalarials notably Quinine, and to a greater extent Quinidine and Halofantrine, are known to prolong ventricular repolarization reflected in prolongation of the electrocardiographic QTc-interval at therapeutic dosages (Nosten, *et al.*, 1993). (White, Looareesuwan and Warrell, 1983) and Halofantrine has been associated with sudden death (Gundersen, Rostrup and Lippe, 1997).

Structure of lumefantrine



Halofantrine is a phenathrene methanol antimalarial drug with blood schizintocidal properties similar to those of quinolone antimalarial .It was developed to treat acute malaria attacks caused by drug resistant strains of p. falciparum but because Halofantrine displays erratic bioavailability potentially lethal cardio toxicity and extensive cross resistance with Mefloquine its use is generally not recommended.(Jatakiya ,*et al.*, 2014).

Lumefantrine is chemically related to Halofantrine, an anti-malarial known to be associated with significant prolongation of QTc interval. Indeed, QTc prolongation is a known class effect of many anti-malarial drugs. As such, cardiac safety has been thoroughly investigated during the preclinical and clinical development of AL. The effects of lumefantrine and its major metabolite desbutyl-lumefantrine on wild-type hERG K+ channels have been investigated in stably transfected human embryonic kidney cells (HEK293) using a whole cell patch-clamp technique (Cousin, Kummerer and Lefèvre, 2008).

Studies carried out by Bindschedler, m in 2002, Andrew in 2009 and in the European journal of Pharmacology show that Coartem has no effect on electrical conductivity of the heart.
Arthmether has no effects on the electrical conductivity of the heart (Norvatis Pharma). Artemether has a short half-life of 2hours as compared to Lumefantrine with a long half-life of 6-8 hours. Any significant effects on electrical conductivity of the heart are due to Lumefantrine which has structural similarity to Halofantrine **(Jatakiya, et al., 2014).**

According to a study done in comparison of acute cardio toxicity of Halofantrine and Lumafantrine in vivo and invitro in anesthetized guinea pigs the results suggested that any direct effects of Halofantrine may have had on the effective refractory period of cardiac muscle and cannot be separated from the vehicle and the prolongation of QTc and consistent observation of AV block with Halofantrine suggesting that in vivo models may be useful for further studies investigating mechanisms underlying cardio toxicity of Lumefantrine (Andrew. J .Batey, *et al.*, 2009).

Also a study done compared cardiac effects of antimalarial Co-artemether and Halofantrine in healthy participants and with Halofantrine the participants showed an increase in QT interval with the length positively correlated to Halofantrine exposure and no such effects was seen with Co-artmether (Binbschedler, *et al.*, 2002).

Cardiac effects of Co-artmether and Mefloquine to healthy volunteers no clinically relevant differences in QTc were observed with lumefantrine in the clinical setting (Eur J C Pharmacol, 2000).

Even a randomized trial to assess the safety, and efficacy of Artmether-Lumefantrine for the treatment of uncomplicated *p*.falciparum malaria no evidence of cardio toxicity during coartem treatment was observed (Rwanda Trans R,2007).

But within the over view of coartem user reviews (FDA Med Watch, 2014) you can gain knowledge and insight about drug treatment with patient discussions assessing coartem information about Artemether/Lumefantrine which may cause a condition that affects the heart rhythm and QT-Prolongation

Besides the contra indications considered like heart failure, slow heartbeat, QTc-Prolongation, family history of certain heart problems all indicate cardiovascular effects caused by Lumefantrine.(Norvatis,*et al.*,2014).

Since Low levels of potassium and magnesium in the blood may also increase your risk of QT-prolongation or the product may contain inactive ingredients which can cause allergic reactions or other problems then evaluation of cardiovascular effects of lumefantrine among patients taking coartem in management of malaria in Bushenyi district.

Cardiac safety

Lumefantrine is chemically related to halofantrine, an anti-malarial known to be associated with significant prolongation of QTc interval. Indeed, QTc prolongation is a known classical effect of many anti-malarial drugs. As such, cardiac safety has been thoroughly investigated during the preclinical and clinical development of AL. The effects of lumefantrine and its major metabolite desbutyl-lumefantrine on wild-type hERG K+ channels have been investigated in stably transfected human embryonic kidney cells (HEK293) using a whole cell patch-clamp technique (Cousin, Kummerer and Lefèvre; 2008).

This *in vitro* hERG channel assay showed that lumefantrine and desbutyl-lumefantrinehave higher IC50 values (approximately 200-fold) than halofantrine. In addition, the calculated cardiac safety indices, which are over 30 for lumefantrine, suggest that lumefantrine and its major metabolite pose an unlikely risk of cardiotoxocity compared with halofantrine (Cousin, Kummerer and Lefèvre; 2008).

As QT correction formulae are based on a normal heart rate of 60 beats/minute, and patients with malaria tend to have elevated heart rates that decrease with successful treatment and defervescence, overcorrection

of the QT interval can also occur. This is even more pronounced in small children, and heart rates higher than 60 beats/minute are routinely seen in healthy children. Despite the changes in QTc associated with malaria, no adverse events attributable to QTc prolongation (e.g. syncope or sudden death) have been reported in clinical trials with AL (Makanga, Premji and Falade; 2006).

Several unrelated drugs have pro-arrhythmic activity associated with an ability to prolong the QT interval of the ECG.

Long QT syndrome, where the rate-corrected QT interval (QTc) of the ECG is abnormally long, may be either congenital in origin, or 'acquired', due to the effects of certain drugs. A diverse range of drugs has been associated with the acquired long QT syndrome and some cause serious cardiac arrhythmias such as torsade de pointes (Napolitano *et al.*, 1994).

Recently, concern has been expressed about the antimalarial drug, halofantrine, following reports of QTc prolongation, episodes of torsade de pointes or sudden cardiac death (Toivonen *et al.*, 1994).

Although some of these adverse events occurred in patients with congenital long QT syndrome (Toivonen *et al.*, 1994), halofantrine-induced QT prolongation also occurred in individuals with normal QT intervals

In addition, adverse effects of halofantrine have been observed in patients receiving standard doses as well as those receiving higher doses (Karbwang *et al.*, 1993), suggesting that this problem may not just be confined to situations of overdose.

A number of other drugs that prolong the QT interval may do so as a consequence of direct actions on cardiac ion channels (Tan *et al.*, 1995). Alternatively, it has been suggested that the precipitation of arrhythmias such as torsade de pointes may result from an abnormal response to alterations in autonomic

control of the heart. Increased adrenergic activity has been implicated in some types of long QT syndrome, whereas some ventricular tachycardias, such as torsade de pointes can be a consequence of preceding bradycardia. Marked hypokalaemia can also cause QT prolongation, trigger torsade de pointes and exacerbate the pro-arrhythmic effects of certain drugs, such as class la antiarrhythmic (Ben-David & Zipes, 1993; Tan *et al.*, 1995). Thus, if halofantrine *per se* does cause QT prolongation a number of different mechanisms may contribute to the development of associated severe arrhythmias like torsade de pointes. In addition, the precipitation of serious arrhythmias may be more likely in the presence of some other confounding factor such as hypokalaemia or bradycardia.

THE LONG QT SYNDROME (LQTS)

The long QT syndrome (LQTS) is causing an abnormality of the heart's electrical system. The mechanical function of the heart is entirely normal. The electrical problem is due to defects in heart muscle cell structures called ion channels. These electrical defects predispose affected persons to a very fast heart rhythm (arrhythmia) called "Torsade de Pointes" (TdP) which leads to sudden loss of consciousness (syncope) and may cause sudden cardiac death.

THE DISEASE NAMED LONG QT SYNDROME

The name of the long QT syndrome refers to the QT-interval measured on the electrocardiogram (ECG or EKG for the German term "Elektrokardiogramm"). Your specialist may refer to long QT syndrome as Romano-Ward syndrome or Jervell, Lange-Nielsen syndrome.

THE QT-INTERVAL

The duration of the QT-interval is a measure of the time required for depolarization and repolarization to occur. In long QT syndrome, the duration of repolarization is longer than normal. Thus, the QT-interval is prolonged.

An interval above 440 milliseconds (msec) is considered prolonged. QT-prolongation in is due to overload of myocardial cells with positively charged ions during ventricular repolarization.

THE CORRECTED QT-INTERVAL (QTc)

The term "corrected" QT-interval may be misunderstood. It does not mean the measured QT-interval is incorrect, but adjusted for heart rate. The reason is that the QT interval is affected by the heart rate. QTc in concept is best compared to the Body Mass Index (BMI).

BORDERLINE QT

Any QTc-interval above 440 milliseconds is considered prolonged.

Borderline QT shows a prolongation of QTc, but not prolonged enough to clearly make the diagnosis.

450 to 470 milliseconds is considered borderline. The average QTc for someone who has long-QT syndrome is 490 milliseconds.

A QTc at or above 480 milliseconds in females or 470 milliseconds in males, is probably a sign for long-QT syndrome, in the absence of drugs, electrolyte disturbance, or other conditions that might independently lengthen the QT-interval.

LONG QT SYNDROME

The disease may be inherited (the genetic form) or acquired

Inherited: Inherited long QT syndrome was first clearly described in 1957. There are two variants, the autosomal dominant Romano-Ward (named by the doctors who first described the disease, O. Connor Ward and C. Romano) type and the autosomal recessive Jervell, Lange-Nielsen (Doctors A. Jervell, F. Lange-Nielsen) type. Inherited long QT syndrome is caused by mutations of at least 9 genes, and possibly more. Five different genes have so far been found. The location of a sixth gene is known, but the actual gene has not been found.

Jervell, Lange-Nielsen is associated with profound deafness and is inherited by autosomal recessive transmission. It occurs when both parents have one of the two genes known to cause Jervell, Lange-Nielsen and a child gets both abnormal genes, one from each parent. Statistically, each child of this couple has a 25% chance of getting both abnormal genes (the "homozygous" state), a 50% chance of getting just one abnormal copy (the "heterozygous" state) and a 25% chance of getting both normal genes and not having long QT syndrome. When a child does get both abnormal genes, they are "homozygous" if both

parents have the same abnormal gene, or "compound homozygous" if one parent has one abnormal gene and the other parent has the second abnormal gene. Jervell, Lange-Nielsen is rare because it is not likely that both parents will have long QT syndrome.

The second and common form of the syndrome is Romano-Ward. In this form the hearing is normal. The patient inherits one abnormal copy of a long QT syndrome gene, and has one normal copy of that gene. It is, therefore, transmitted by autosomal dominant inheritance. Each child born to an affected parent has a 50% chance of receiving the abnormal copy and a 50% chance of receiving the normal copy.

ACQUIRED LONG QT SYNDROME

Acquired long QT syndrome is most often due to the administration of medication. These medications are contraindicated in patients with the long QT syndrome, and a subsequent section will identify these drugs.

INHERITED LONG QT SYNDROME

The frequency is unknown but it appears to be a common cause of sudden and unexplained death in children and young adults. It is certainly much more common than previously thought. It may be as frequent as 1 in 5000 to 7000. This means, one of 5000 to 7000 new-borns have the disease. The Jervell, Lange-Nielsen form is rare, but the Romano-Ward variant is being recognized with increasing frequency. In the USA, the presence of long QT syndrome is estimated to affect about 50.000 people and to cause as many as 3000 deaths each year. It is present in all races and ethnic groups, but it is not certain if the frequency is the same in all races.

The usual symptoms are syncope (sudden loss of consciousness) or sudden death, typically occurring during physical activity or emotional upset. These most commonly begin in preteen to teenage years, but may present from a few days of age to middle age. The syncopal episodes are often misdiagnosed as the common faint (vasovagal event) or a seizure. Actual seizures are uncommon in long QT syndrome, but epilepsy is one of the common errors in diagnosis. Sudden loss of consciousness during physical exertion or during emotional excitement should strongly raise the possibility of the long QT syndrome.

A family history of unexplained syncope or sudden death in young people should also raise suspicion. Importantly, about one third of individuals who have the long QT syndrome never exhibit symptoms, and therefore, the lack of symptoms does not exclude a person or family from having long QT syndrome. Any

young person that has an unexplained cardiac arrest should be considered for long QT syndrome, as well as those with unexplained syncope.

SYMPTOMS

Patients with long QT syndrome develop a very fast heart rhythm disturbance known as "Torsade de pointes". This is a form of ventricular tachycardia. This rhythm is too fast for the heart to beat effectively, so the blood flow to the brain falls precipitously causing the sudden loss of consciousness. In most instances, there is no warning prior to syncope.

Recently, a scheme for risk stratification among (untreated) patients with long-QT syndrome according to sex, genotype and prolongation of the QT-interval has been proposed.

Risk for cardiac event*	**QTc at rest**	**Genotype**	**Sex**
High (over 50%)	over 500 msec		

The Electrocardiogram shows P, Q, R, S, T waves. They are electrical voltages generated by the heart and recorded by the electrocardiograph from the surface of the body .**P** wave is caused by the spread of depolarization through the atria and this is followed by atrial contraction which causes a slight rise the atrial pressure immediately after the P wave. About 0.16 second after the onset of the P wave, the **QRS** a wave appear as a result of depolarization of the ventricles and causes the ventricular pressure to begin rising.QRS complex begin slightly before the onset of ventricular systole. Finally the ventricular **T** wave is observed in the electrocardiogram which represents the stage of repolarization of the ventricles at which time the ventricular muscle fibers begin to relax (Guyton &Hall, 9TH edition pg110).

The long QT syndrome is causing an abnormality of the heart's electrical system. The mechanical function of the heart is entirely normal. The electrical problem is due to defects in heart muscle cell structures called ion channels. These electrical defects predispose affected persons to a very fast heart rhythm (arrhythmia) called "*Torsade de Pointes*" which leads to sudden loss of consciousness and may cause sudden cardiac death

CHAPTER THREE

3.0 Methods and Materials

3.1.0 Study design

The study was a quantitative prospective randomized study involving monitoring electrocardiograms of *P. falciparum* infected malaria patients on coartem treatment. This study was performed according to the Declaration of Helsinki for bio-medical research involving human subjects and the rules of Good Clinical Practices (ICH Harmonized Guideline for GCP, 1996).

3.1.1 Study setting

The study was conducted among malaria patients attending KIU-TH in Bushenyi district.

3.1.2 Study population

The patients were selected randomly conducted in adults 18years old and above presenting with uncomplicated P.falciparum in Bushenyi district.

3.1.3 Sample size

Slovin's formula was used to estimate population sample size for malaria Patients.

$$n = \frac{N}{1 + N(e)^2}$$

Where n is the sample size, N is the population size and e is the level of precision /marginal error which is 5% while 1 is constant. *(Source; Guilford J.P. and Frucher B, 1973)*

A sample size of 176 patients was obtained using a prevalence of 315 calculated from the previous three months of July, August and September. Only 5 patients were involved in this study.

3.1.4 Inclusion criteria

Patients diagnosed with P.falciparum malaria, without any cardiac problems were selected,

Male and female subjects of at least 18yrs and body weight±15%of_ideal weight (minimum50kg) as related to height and body frame.

Subjects with normal findings as determined by baseline past medical History, physical examination and vital signs (blood pressure, pulse rate), Cardiac markers and oxygen saturation.

3.1.5 Exclusion criteria

Patients not diagnosed with P.falciparum malaria, with existing cardiac problems.

History of cardiovascular, renal, hepatic, ophthalmic, pulmonary, neurological, metabolic, psychiatric diseases or any malignancy.

History of recent myocardial infarction, cardiac arrhythmias, cardiac failure.

History of hypersensitivity to artemether/Lumefantrine combination.

3.1.6 Sampling techniques

Random sampling of the patients was done. Using check lists ruled out any exceptions.

3.1.7 Data collection procedures

- Use check lists to fill in whatever was done
- Monitor vital signs Temperature, blood pressure, Respiratory rate , Pulse rate
- Laboratory diagnosis of *plasmodium falciparum* parasites.
- Informed Consent taken from the patient
- Baseline Electrocardiograms were recorded before dosing.
- After giving informed consent patients were given Artemether/ Lumefantrine (20mg/120mg) adult dose 4tables twice daily for 3days.
- Electrocardiographic monitoring after fifth dose.
- Electrocardiographic intervals were measured automatically by the machine and evaluate

CHAPTER FOUR

4.0 RESULTS

Table I: showing baseline ECG results

Patient	gender	Age(yrs.)	Wt.(kg)	HR (bpm)	PR int (ms)	QRS int(ms)	QT int(ms)	QTc int(ms)
1	F	23	54	65	130	106	373	387
2	M	27	63	61	149	107	374	398
Normalvalues				60-100	120-200	<120	<420	380-420

Wt.-weight HR-heart rate int- interval NV- Normal Values

Fig I: Normal ECG-ELECTROCARDIOGRAM

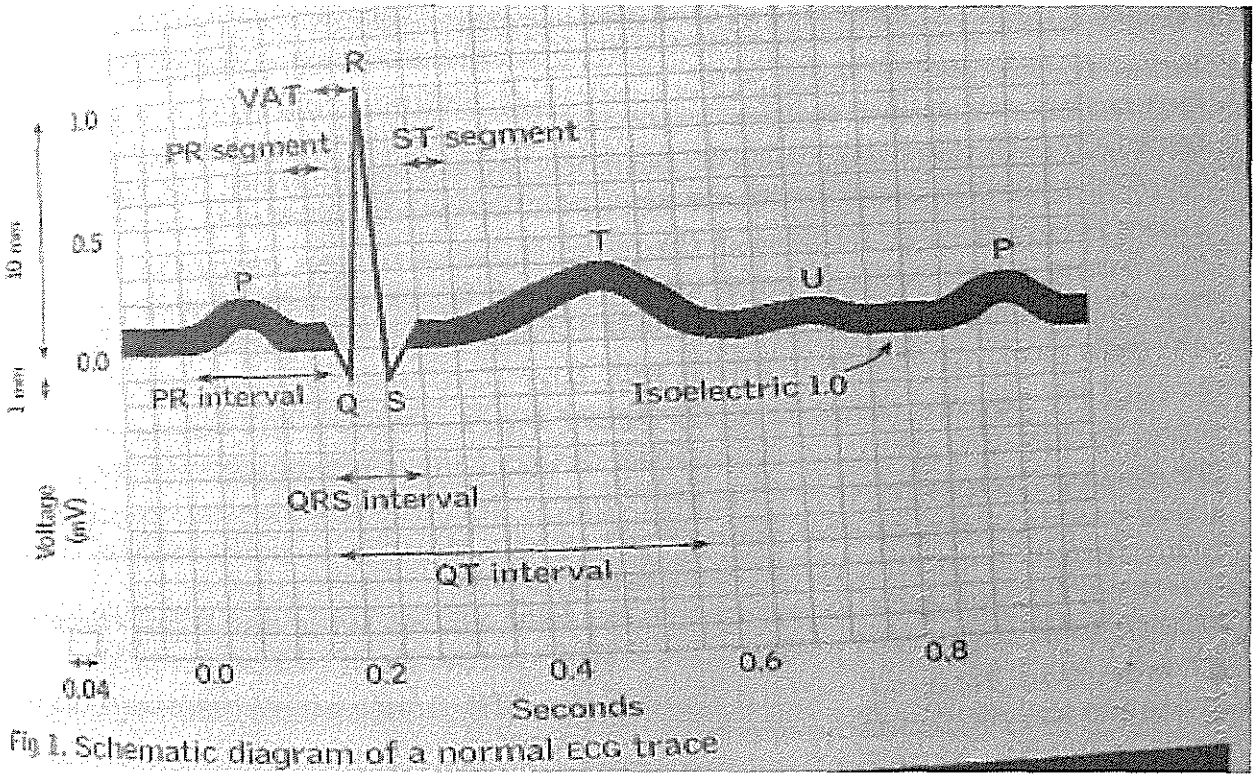


Fig 1. Schematic diagram of a normal ECG trace

Ref: oxford hand book of clinical medicine, eighth edition, page: 91

The Electrocardiogram shows P, Q, R, S, T waves. They are electrical voltages generated by the heart and recorded by the electrocardiograph from the surface of the body .P wave is caused by the spread of depolarization through the atria and this is followed by atrial contraction which causes a slight rise the atrial pressure immediately after the P wave. About 0.16 second after the onset of the P wave, the QRS a wave appear as a result of depolarization of the ventricles and causes the ventricular pressure to begin rising.QRS complex begin slightly before the onset of ventricular systole. Finally the ventricular T wave is observed in the electrocardiogram which represents the stage of repolarization of the ventricles at which time the ventricular muscle fibers begin to relax (Guyton &Hall, 9TH edition pg110).

Fig II: Baseline Electrocardiogram of the patient

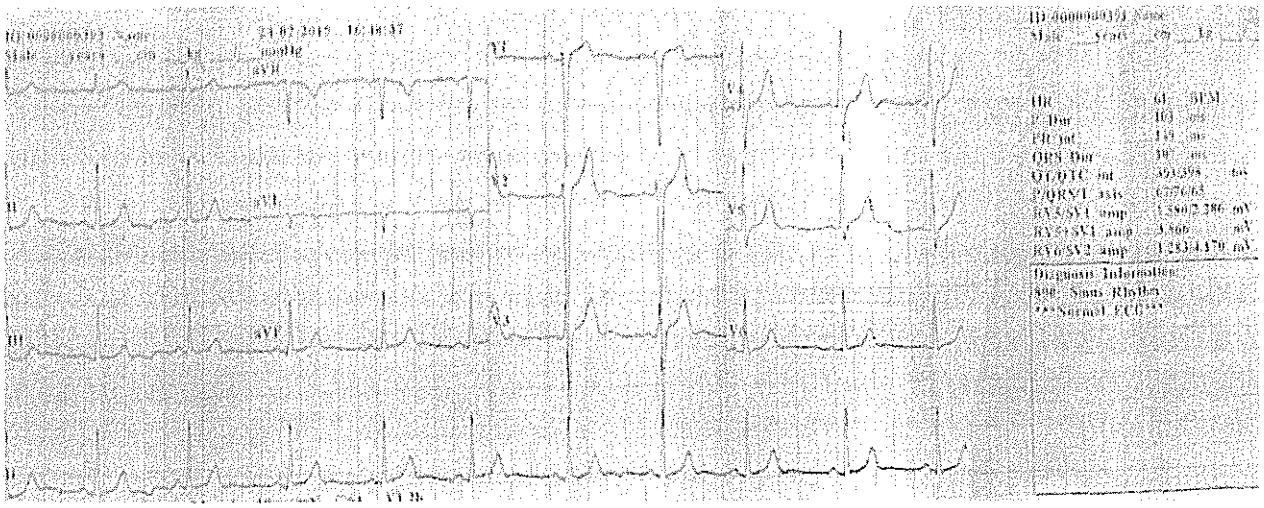


Table II: showing ECG for 74 year old male patient

Patient	Age	Weight	Heart rate	PR interval	QRS interval	QT interval	QTc interval
Baseline	74	62	58	149	120	437	432
2nd ECG			72	149	112	418	460
Normal values			60-100	120-200	<120	<420	380-420

Wt.-weight HR-heart rate int- interval NV- Normal Values

The ECG record was for a male known hypertensive malaria patient from MOPD with baseline QTc interval of 432 milliseconds which was in the normal range and second ECG 460 milliseconds which is a border line QTc interval.

450 to 470 milliseconds is considered borderline. The average QTc for someone who has long-QT syndrome is 490 milliseconds.

An interval above 440 milliseconds (msec) is considered prolonged. QT-prolongation in is due to overload of myocardial cells with positively charged ions during ventricular repolarization.

The alternative hypothesis is rejected.

The risk of QT prolongation can be increased by certain medical conditions or use of other drugs that affect the heart rhythm (FDA Med Watch 2014).

Table III: showing ECG for 23 year old female patient

Patient	Age	Weight(Kg)	Heart rate	PR int	QRS int	QT int	QTc int
Base line	23	54	74	138	97	373	393
2nd ECG			74	143	96	359	414
Normal values				120-200	<120	<420	380-420

Wt.-weight HR-heart rate int- interval NV- Normal Values

The ECG records are for a 23 female malaria patient with no chronic disease had a baseline normal QTc interval of 393 milliseconds and second QTc interval of 414 milliseconds

A QTc at or above 480 milliseconds in females or 470 milliseconds in males, is probably a sign for long-QT syndrome, in the absence of drugs, electrolyte disturbance, or other conditions that might independently lengthen the QT-interval.

Table IV: showing ECG for 24 year old male patient

Patient	Age	Weight	Heart rate	PR int	QRS int	QT int	QTc int
Baseline	24	71	65	130	108	374	390
2ND ECG			65	136	104	378	393
Normal values				120-200	<120	<420	380-420

Wt.-weight HR-heart rate int- interval NV- Normal Values

The ECG records were in a 24 *p.falciparum* infected malaria patient with normal baseline QTc interval of 390ms and normal second QTc interval of 393ms

A QTc at or above 470 milliseconds in males, is probably a sign for long-QT syndrome, in the absence of drugs, electrolyte disturbance, or other conditions that might independently lengthen the QT-interval.

Table V: showing ECG for 20 year old female patient

Patient	Age	Weight(Kg)	Heart rate(bpm)	PR interval	QRS interval	QT interval	QTc interval
Baseline		61	76	177	100	346	391
2ND ECG			82	181	112	353	414
Normal values				120-200	<120	<420	380-420

Wt.-weight HR-heart rate int- interval NV- Normal Values

The ECG record in a 20 year old female malaria patient with QTc intervals in the normal range.

A QTc at or above 480 milliseconds in females is probably a sign for long-QT syndrome, in the absence of drugs, electrolyte disturbance, or other conditions that might independently lengthen the QT-interval.

Table VI: showing ECG for 28 year old male patient

patient	age	weight	Heart rate	PR interval	QRS interval	QT interval	QTc interval
Baseline	**28**	**60**	**54**	**149**	**109**	**383**	**360**
2^{ND} ECG			**64**	**158**	**104**	**372**	**385**
Normal values				**120-200**	**<120**	**<420**	**380-420**

Wt.-weight HR-heart rate int- interval NV- Normal Values

The ECG record in a 28 year old male malaria patient with normal QTc intervals. On addition to coartem he took ciprofloxacin indicated in urinary tract infections.

A QTc at or above 470 milliseconds in males, is probably a sign for long-QT syndrome, in the absence of drugs, electrolyte disturbance, or other conditions that might independently lengthen the QT-interval.

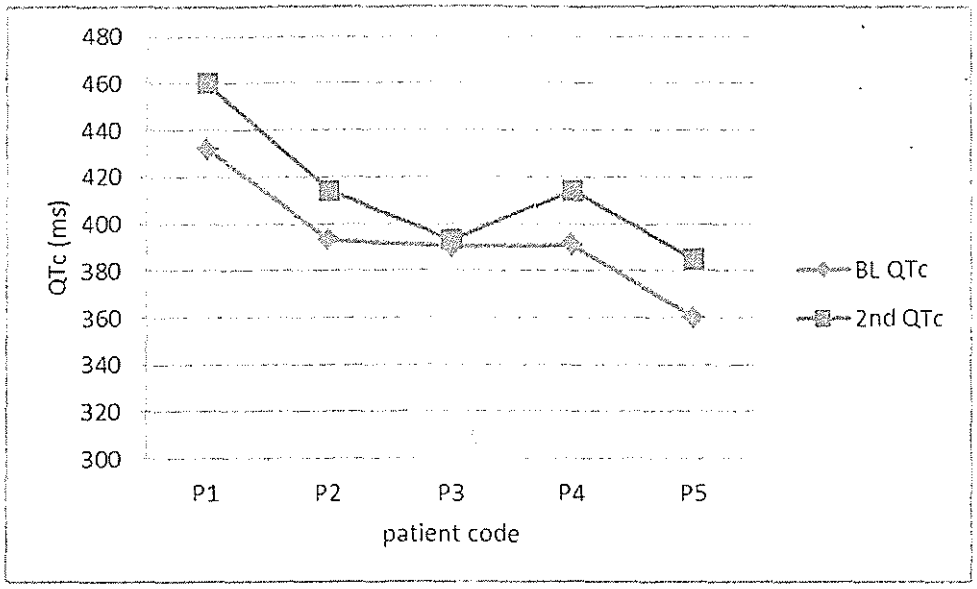
The risk of QT prolongation can be increased by certain medical conditions or use of other drugs that affect the heart rhythm (FDA Med Watch 2014)

Table VII: showing QTc and HR for the patients

	P1	P2	P3	P4	P5
BL QTc	432	414	390	391	360
2^{nd} QTc	460	401	393	414	385
BL HR	58	74	65	76	54
2nd HR	72	74	65	82	64

QT intervals vary with heart rate and the corrected QTc is obtained using Bazzet's formula ,QTc=QT/RR1/2

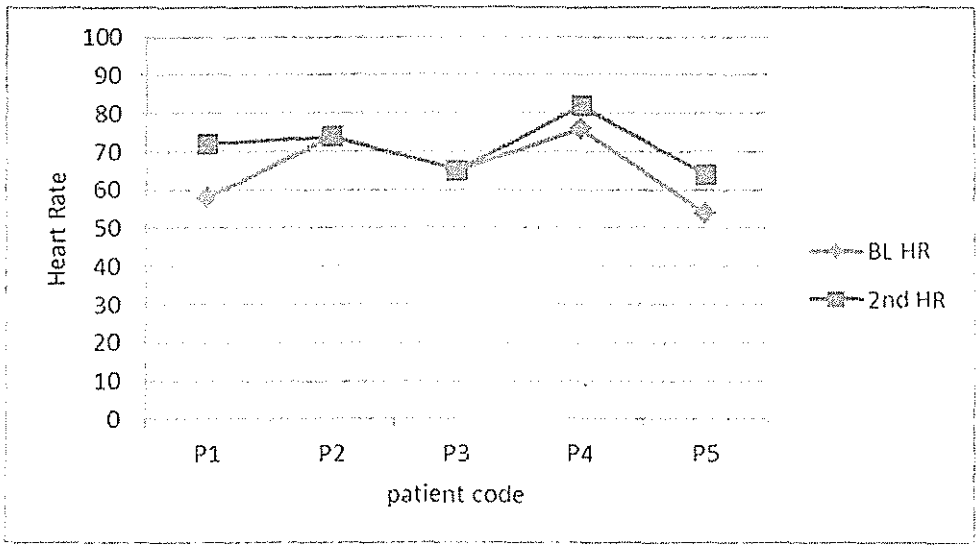
Fig III: A graph showing QTc for the patients



Base line QTc intervals were normal with in the normal range of 380-420milliseconds

The second QTc intervals were normal with the exception of one border line QTc interval of 460 milliseconds as a result of hypertension in a 74 year old male

Fig IV: A graph showing HR for the patients



QTc interval varies with heart rate.

The heart rates were normal with in the normal range of 60-100beatsperminute

Heart rate reduces with age due to decreased activity of the cardiac muscles.

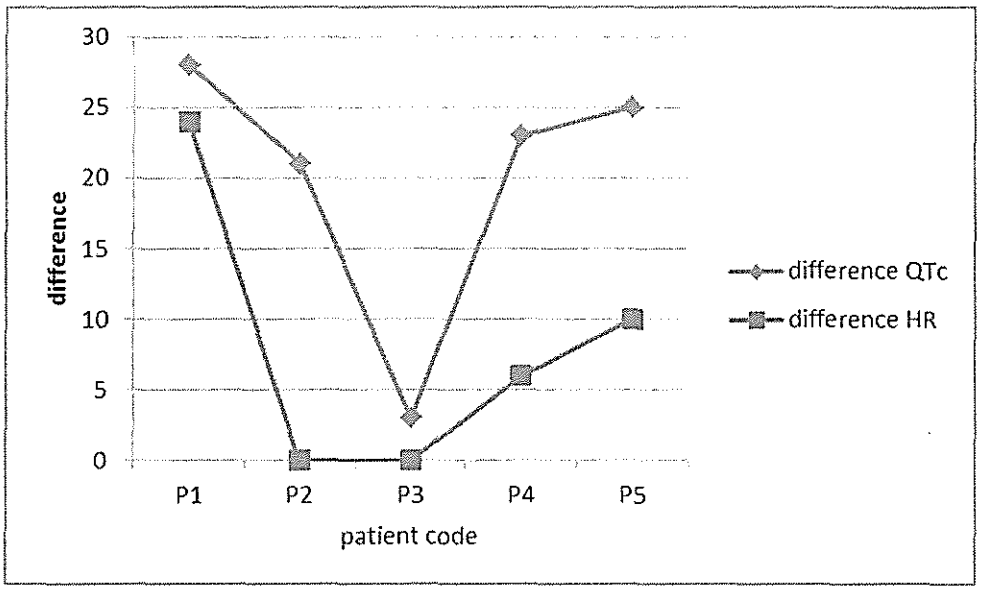
Table VIII: showing difference in QTc and HR for the patients

	P1	P2	P3	P4	P5
difference QTc	28	21	3	23	25
difference HR	14	0	0	6	10

No clinically relevant differences in QTc intervals were observed after sequential administration of Artemether/Lumefantrine(Coartem)

No correlation between the length of the QTc interval in malaria patients and their corresponding heart rates

Fig V: A graph showing the difference in QTc and HR for the patients



No clinically relevant differences in QTc intervals were observed after sequential administration of Artemether/Lumefantrine(Coartem)

As QT correction formulae are based on a normal heart rate of 60 beats/minute, and patients with malaria tend to have elevated heart rates that decrease with successful treatment and defervescence, overcorrection of the QT interval can also occur. Despite the changes in QTc associated with malaria, no adverse events attributable to QTc prolongation (e.g. syncope or sudden death)

DISCUSSION

There is an increase in the heart rates and decrease in QTc intervals for the patients who were being treated with Coartem® for uncomplicated malaria at KIU-TH. The results were similar to a study (by Margaretha, 2002) in which she compared the cardiac effects of coartemether/lumefantrine and she showed that heart rates and QTc intervals were comparable after treatment with halofantrine and coartemether, and no clinically relevant study drug-related changes in heart rate were observed after either treatment. But realized that there was a marked degree of inter-individual variability in Coartem® administration. In this study, the variations in QTc intervals ranged between 3ms and 25ms while heart rate changes ranged between -6bpm and 0bpm.

These changes are thought to be caused by the effects of the lumefantrine on the QTc interval in the cardiac cycle as it has already been documented. In the previous literature, artemether is shown not to cause any significant change in the QTc interval and not have any effects on the heart rate irrespective of the dosage administered (Matson, 1999). Another common cause of these QTc variations could also be due to electrolytes disturbance caused by the malaria itself. (Bakshi, 2000) Showed that hyperparasitemia in malaria especially within the tropical region was highly associated with disturbance in electrolyte levels, in this he explained that could be due to fevers and vomiting.

Much as these patients were put on the same dosage of artemether-lumefantrine concentration, the results showed that there were individual variations in the change in QTc intervals. Previous studies had demonstrated that there is no correlation between the cardiac effects and dosage of artemether-lumefantrine (Veenendaal, 1991).

Much as there have been observed changes in the QTc intervals resulting from the treatment of malaria with Coartem®, fatal changes in QTc intervals were not observed in this study and all the changes were still within the safety levels for the use of coartem® (Novartis, 2009).

The highest change in QTc interval in this study was 23ms, and the highest change in heart rate was 0bpm. These observed changes were still within the ranges of acceptable levels that were available in the literature.

The Lumefantrine caused QTc prolongation had been previously reported after high-dose intramuscular treatment with Artemether-Lumefantrine in animal experiments and in a clinical study in patients with severe malaria. In this study, the cardiac effects of six oral doses of 80/480 mg Artemether-Lumefantrine, an antimalarial known to prolong the QTc interval according to previous literature were believed to be the major causes of variations in the pulse rates of the subjects observed in this study.

The study further showed that there were variations in the QTc intervals of the patients, the findings could be due to the fact that the age of the study subjects varied and thus there were variations heart rates, PR intervals, QT intervals and QTc intervals and the most important cause of these could be differing ages and gender among the study subjects.

Artemether-Lumefantrine may cause rapid pulse rate (first sign that a side effect is occurring) according to the technical guidelines provided about Coartem® from previous literature, though, this study shows that the side effects were not too high to cause fatal effects on the patients undergoing treatment using Artemether-Lumefantrine (Coartem®).

The alternative hypothesis stating that Artemether/Lumefantrine possesses significant effect on electrical conductivity of the heart has not been supported.

No significant observation suggestive of cardio toxicity was noted in the study.

There has been natural concern over the cardio toxic potential of newly introduced antimalarial drugs since the unexpected discovery of the marked effects of halofantrine on ventricular repolarization, well after it had been introduced in clinical practice (Touze *et al., 1996).*

Electrocardiogram QT prolongation is a well-known risk factor for proarrhythmic events, including sudden death. Lumefantrine is an aryl-amino alcohol antimalarial with some structural similarities to halofantrine. It is also, like halofantrine, lipophilic and hydrophobic, with very variable oral bioavailability leading to considerable inter-individual variability in plasma concentrations.

Van Vugt *et al.*, 1999 reported no evidence for clinically significant changes in the electrocardiographic intervals and in particular no relationship between plasma concentrations of lumefantrine and QTc prolongation. But postmarket survillence remains a continuous processes in drug discovery as more toxic effects could be discovered later in clinical use of the drugs for instance Thalidomide was discovered to be

teratogenic during clinical use and also pioglitazone an antidiabetic agent was found to cause serious cardiovascular effects which led to its withdraw from market..

Suhas *et al.*, 2010 reported no significant observation suggestive of cardio toxicity with Artemether and Lumefantrine treatment of uncomplicated malaria.

In the drug monograph of Novartis Pharma, AG (2011), there have been no reports of clinical adverse effects attributable to QTc prolongation (e.g. syncope, sudden death),

Not considering any compromise with their findings, the study results had no clinically relevant differences in QTc intervals observed after sequential administration of Artemether/Lumefantrine among patients with uncomplicated malaria.

Conclusion

The test product can be used as a therapeutic option with likely better patient compliance in the treatment of uncomplicated *P.falciparum* malaria.

Recommendation

- Further study on effects of coartem on electrical conductivity of heart in patients who were treated with Intravenous quinine.
- Further study on the topic laying strategies on taking second ECG.
- Study including a larger number of study subjects and following these subjects for a longer duration of time using varying dosages should be conducted to evaluate the effects of coartem® on electrical conductivity of the heart at Kampala International University-Teaching Hospital.

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APPENDICES

APPENDIX I:

PROJECT BUDGET

ITEM/SERVICE	QUANTITY	UNIT PRICE(shs)	TOTAL COST(shs)
SPHIGMOMANOMETER (B.P Unit Aneroid Adult Cuff)	1	103,000/=	103,000/=
STETHOSCOPE (Cardio-double Head harveyelite)	1	348,000/=	348,000/=
ELECTROCARDIOGRAM	1		
THERMOMETER	1	9,000/=	9,000/=
WATCH	1	20,000/=	20,000/=
NOTE BOOK	2	2,000/=	2,000/=
PENS	2	1,000/=	1,000/=
LAPTOP	1	1,500,000/=	1,500,000/=
TOTAL COSTS			2,489.000/=

APPENDIX II:

WORK PLAN

ACTIVITY	Jun-14	Jul-14	Aug-14	Sep-14	14-Oct	14-Nov	14-Dec
Proposal writing							
Proposal Defense							
Data collection and analysis							
Dissertation writing and defense							

CONSENT FORM

STUDY TITLE: EVALUATION OF THE EFFECT OF COARTEM ON THE ELECTRICAL CONDUCTIVITY OF THE HEART IN KIU-TH BUSHENYI DISTRICT

INVESTIGATORS: DR. OKORUWA G., DR. DARFIEWHARE OE., MR. EZEONUMWELU J, DR. RUHAKANA .M. and MISS BABIRYE P. of Kampala International University- Western Campus, Ishaka. **Tel. +256788727434 & +256702327482**

The above researchers are studying the effects of Coartem on the electrical conductivity of the heart.

You are hereby invited to voluntarily participate in the study where the electrical activity studies shall be undertaken on you prior and when taking your antimalarial medication (Coartem). The examinations are non-invasive and shall not involve taking any specimen from you.

This study is being done to find out if Coartem has any effect on the electrical conductivity of the heart because many people who suffer from Malaria use it as one of the nationally recommended first-line medication in Uganda.

Your benefits as a participant include free heart check and free genuine Coartem

You are free to accept or withdraw from the study any time during the study. All study findings shall be treated with highest confidentiality and will be used strictly for research purpose.

Please sign the space below if you accept to participate in this study.

I..... ....., the principles and activities in this study have been explained to me in the language I understand, after carefully understanding the procedures; hereby voluntarily agree to participate in this study.

Name of participant	signature	date
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KAMPALA INTERNATIONAL UNIVERSITY
EXPLORING THE HEIGHTS

SCHOOL OF PHARMACY

October 15, 2014
THE PRINCIPAL
KIU-TEACHING HOSPITAL
WESTERN CAMPUS.

Dear Sir,

RE: REQUEST FOR PERMISSION TO USE THE HOSPITAL ECG FACILITY TO EVALUATE THE CARDIOVASCULAR EFFECT OF LUMEFANTRINE ON PATIENTS (KIU COMMUNITY) PRESENTING WITH MALARIA

I am writing to seek your permission to use the hospital faciiity to conduct a research on the effect of lumefantrine (a component of lumefantrine/arthemisinine) on the Electrical Conductivity of the heart. The researchgroup is composed of Dr. Dafiawhere Ephraim of the Department of Medicine KIUTH, Pharmacist Ezeonwumelu Joseph of the School of Pharmacy.Ms PhionaBibirye and Dr. Godwin Okoruwa
The research intends to recruit patients diagnosed to have malariaby KIUTH clinicians. The intention is to start by first week of November 2014.

EXECUTIVE SUMMARY

Several unrelated drugs have pro-arrhythmic activity associated with an ability to prolong the QT-interval of the Electrocardiogram just as proved for Halofantrine (2012). Lumefantrine has some chemical similarities to Halofantrine, an antimalarial known for QTc prolongation; due to their structural similarities the cardiac effect on electrical conductivity of the heart by Lumefantrine remains a matter of debate in therapeutics. This research aims at evaluating the cardiovascular effects of Lumefantrine component of coartem in patients taking coartem in management of malaria in KIU community..

Method: The research will be performed in a randomized parallel group designfor a period of one month. Safety assessment will be done by monitoring vital signs, blood pressure, Heart rate, Oxygen saturation

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and monitoring of Electrical conductivity. Electrocardiograms will be recorded before dosing and repeatedly thereafter.

The Bazett formula will be used to calculate the QTc interval. The maximum and average QTc intervals for the first, third and sixth dosing intervals of co-artemether treatment will be compared among treatments over 60hours.

Thank you.

Yours Sincerely,

Dr. Godwin Okoruwa
DEAN/SENIOR LECTURER
SCHOOL OF PHARMACY

Recommended & forwarded
To the HOD - A&E
Please allow Dr. Dafewaine to
use the ECG machine in A&E
Thanks.